REMARKS

In response to the above-identified Office Action ("Action"), Applicants traverse the Examiner's rejection to the claims and seek reconsideration thereof. Claims 1-12 are pending in the present application. Claims 11 and 12 remain withdrawn. In this response, claims 1, 3-5, 8, 10 and 11 are amended, claims 2 and 7 are cancelled and no claims are added.

I. Claim Amendments

Applicants respectfully submit herewith amendments to claims 1, 3-5, 8, 10 and 11. Applicants respectfully submit the amendments do not add new matter and are supported by the specification. Accordingly, Applicants respectfully request consideration and entry of the amendments to claims 1, 3-5, 8, 10 and 11.

II. Claim Rejections – 35 U.S.C. §112

A. In the outstanding Action, claims 1 and 4-9 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Claim 1 is amended to recite that "a prostaglandin $F_{2\alpha}$ derivative" is "at least one member selected from the group consisting of latanoprost, isopropyl unoprostone, travoprost or bimatoprost." Applicants believe in view of the amendments to claim 1, claims 1 and 4-9 are in compliance with 35 U.S.C. §112, first paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection of the claims on this basis.

B. In the outstanding Action, claims 1 and 4-10 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is cancelled therefore the rejection of claim 7 on this basis is moot. Claim 1 is amended as previously discussed to further define the term "derivative." Claim 10 is amended to replace the term Miglyol with "medium chain fatty acid triglyceride." Applicants believe in view of the amendments to claims 1 and 10, claims 1, 4-6 and 8-10 are in compliance with 35

U.S.C. §112, second paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection of the claims on this basis.

III. Claim Rejections – 35 U.S.C. §102

In the outstanding Action, claims 1, 4, 6, 8 and 9 are rejected under 35 U.S.C. §102(b) as being unpatentable over U.S. Patent No. 5,767,153 issued to Bowman et al. ("Bowman").

It is axiomatic to a finding of anticipation that each and every element of the rejected claim be found within a single prior art reference.

Independent claim 1 provides the following:

> 1. A pharmaceutical composition comprising an oil-in-water emulsion containing a ***prostaglandin $F_{2\alpha}$ derivative, which is at least one member selected from the group consisting of latanoprost, isopropyl unoprostone, travoprost and bimatoprost***, an oil, a water-soluble polymer and water.

Applicants respectfully submit that Bowman fails to teach each of the elements of claim 1. In particular, Bowman fails to teach "an oil-in-water emulsion containing a prostaglandin $F_{2\alpha}$ derivative, which is at least one member selected from the group consisting of latanoprost, isopropyl unoprostone, travoprost and bimatoprost" as recited in amended claim 1.

Bowman discloses a sustained release topical ophthalmic composition. The Patent Office alleges that Bowman discloses a composition including an oil (claim 6), a water soluble polymer (claim 4), water and a prostaglandin $F_{2\alpha}$ derivative ($PGF_{2\alpha}$ -1-Isopropyl Ester, col. 5, Table 1). Bowman describes PGFs as an example of oily medicaments, however, does not specifically disclose PGFs selected from at least one of latanoprost, isopropyl unoprostone, travoprost and bimatoprost as recited in claim 1.

Since Bowman fails to teach each and every element of claim 1, claim 1 is not anticipated by the cited prior art reference. Applicants respectfully request reconsideration and withdrawal of the rejection of claim 1 under 35 U.S.C. §102 over Bowman.

In regard to claims 4, 6, 8 and 9, these claims depend from claim 1 and incorporate the limitations thereof. Thus, for at least the reasons that claim 1 is not anticipated by Bowman, claims 4, 6, 8 and 9 are further not anticipated by the cited prior art reference. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 4, 6, 8 and 9 under 35 U.S.C. §102 over Bowman.

IV. Claim Rejections – 35 U.S.C. §103

A. In the outstanding Action, claims 2, 3 and 5 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bowman in view of U.S. Patent No. 6,342,524 issued to Hellberg et al. ("Hellberg").

To establish a *prima facie* case of obviousness, the Examiner must set forth "some articulated reasoning with some rational underpinning to support the conclusion of obviousness." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007). In combining prior art elements to render the claimed combination of elements obvious, the Examiner must show that the results would have been predictable to one of ordinary skill in the art. See *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103*, Section III(D), issued by the U.S. Patent and Trademark Office on October 10, 2007.

Claims 2, 3 and 5 depend from claim 1 and incorporate the limitations thereof. For at least the reasons previously discussed, Bowman fails to disclose or render predictable at least the elements of "an oil-in-water emulsion containing a prostaglandin $F_{2\alpha}$ derivative, which is at least one member selected from the group consisting of latanoprost, isopropyl unoprostone, travoprost and bimatoprost" as incorporated into claims 2, 3 and 5 from claim 1. Rather, Bowman describes PGFs as an example of oily medicaments and does not specifically disclose PGFs selected from at least one of latanoprost, isopropyl unoprostone, travoprost and bimatoprost. Moreover, Bowman is silent about the stability of the PGFs in the emulsion.

One of ordinary skill in the art would further not understand to modify Bowman to include a PGF such as latanoprost in view of the teachings of Hellberg. As is well understood in the art, PGFs such as latanoprost typically have poor solubility and are chemically unstable when combined with an aqueous solution. Moreover, as can be seen from the comparison of the

claimed formulation (including latanoprost) to Xalatan (a non-oil-in-water emulsion which includes latanoprost) in Table 2, the chemical degradation of PGF is suppressed by the claimed formulation beyond even that of an emulsion that is not oil-in-water. As disclosed on page 13 of the Application, the chemical degradation of PGF is suppressed in the oil-in-water emulsion by combining the claimed PGFs with an oil (e.g., a medium chain fatty acid triglyceride) and a water-soluble polymer as recited in claim 1. See Application, page 13 and Table 2. These are clearly results which were not achieved or expected by the prior art formulations.

Neither Bowman nor Hellberg describe an oil-in-water emulsion in which the chemical stability of the claimed PGFs could be maintained. Therefore, even if the references could be combined, they would not render an oil-in-water emulsion including the claimed PGFs obvious. In particular, Bowman is silent regarding the stability of the PGFs in the disclosed emulsions. Hellberg discloses a topical ophthalmic composition comprising prostaglandin analogs and prostaglandin synthesis inhibitors. Applicants acknowledge that the PGFs latanoprost and travoprost are described in Hellberg. The reference, however, fails to disclose an oil-in-water emulsion containing latanoprost or travoprost and is silent about medium chain fatty acid triglycerides, which as previously discussed maintain the stability of the PGF in the emulsion. Thus, since one of ordinary skill in the art would understand the claimed PGFs to be incompatible with an oil-in-water emulsion and the references do not teach otherwise, one of ordinary skill in the art would not understand to modify Bowman in view of Hellberg to arrive at the claimed combination of elements. Thus, for at least the foregoing reasons claims 2, 3 and 5 are not *prima facie* obvious over Bowman and Hellberg. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 2 and 12 under 35 U.S.C. §103 in view of Bowman and Hellberg.

Therefore, there is no motivation to combine Bowman and Hellberg.

B. In the outstanding Action, claims 7 and 10 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bowman in view of U.S. Patent No. 6,635,654 issued to Chang et al. ("Chang").

Claim 7 is cancelled therefore the rejection of claim 7 on this basis is moot.

Claim 10 provides the following:

> 10. An eye drop which is an oil-in-water emulsion, comprising latanoprost, medium chain fatty acid triglyceride, polyvinyl alcohol and water.

For at least the reasons previously discussed, Bowman fails to disclose "an oil-in-water emulsion, comprising latanoprost, medium chain fatty acid triglyceride, polyvinyl alcohol and water" as recited in claim 10.

Chang further fails to cure the deficiencies of Bowman with respect to each of these elements. Chang discloses an aqueous ophthalmic emulsion comprising loratadine, a fatty acid ester and a surfactant. Miglyol 810N is used as the fatty acid ester for preparation of the emulsion. Loratadine is an azatadine derivative, as shown in the AHFS Drug Information 2001, page 36 "Loratadine" attached hereto. Loratadine, therefore, is quite different from the prostaglandin F derivatives in chemical structure (benzocyproheptapylidine tricyclic ring structure), chemical properties (crystalline powder) and physiological activity (antihistamine). Thus, even if it were possible to find that Miglyol is an oil suitable for the emulsion of loratadine, since loratadine and the claimed PGFs are entirely different, one of ordinary skill in the art would not understand Miglyol to be suitable for the stable emulsion of the claimed prostaglandin derivatives. Accordingly, upon review of Bowman which does not disclose any medium chain fatty acid and Chang which fails to recite an oil-in-water emulsion containing $PGF_{2\alpha}$ derivative, one of ordinary skill in the art would not find it obvious to arrive at the formulation of claim 10.

For at least the foregoing reasons, Bowman and Chang fail to disclose or render predictable each and every element of claim 10. Since each of the elements of claim 10 is not found within the cited prior art references, a *prima facie* case of obviousness may not be established. Applicants respectfully request reconsideration and withdrawal of the rejection of claim 10 under 35 U.S.C. §103 in view of Bowman and Chang.

CONCLUSION

In view of the foregoing, it is believed that all claims now pending, namely claims 1, 3-6 and 8-12, are now in condition for allowance and such action is requested at the earliest possible date. If there are any additional fees due in connection with the filing of this response, please charge those fees to our Deposit Account No. 02-2666. Questions regarding this matter should be directed to the undersigned at (310) 207-3800.

Respectfully submitted,

BLAKELY, SOKOLOFF, TAYLOR, & ZAFMAN LLP

Dated: 3/2/10

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CERTIFICATE OF TRANSMISSION

I hereby certify that this correspondence is being submitted electronically via EFS Web on the date shown below to the United States Patent and Trademark Office.

Nedy Calderon 3/3/10

Nedy Calderon Date

AHFS DRUG INFORMATION 2001

American Society of Health-System Pharmacists®

■ Dosage in Renal and Hepatic Impairment

Adjustment of fexofenadine hydrochloride dosage may be necessary in patients with renal impairment. Peak plasma fexofenadine concentrations increased by 87 or 111%, and elimination half-life increased by 59 or 72% in patients with mild (e.g., creatinine clearance of 41–80 mL/minute) or severe (creatinine clearance of 11–40 mL/minute) renal impairment, respectively, when compared with those observed in healthy individuals. In addition, peak plasma fexofenadine concentration increased by 82% and elimination half-life increased by 31% in those on hemodialysis (creatinine clearance of 10 mL/minute or less) compared with healthy individuals. Therefore, the manufacturer states that adults and children 12 years of age and older with impaired renal function or those on hemodialysis should receive an initial fexofenadine hydrochloride (either when given alone or in fixed combination with pseudoephedrine hydrochloride) dosage of 60 mg daily. Children 6 to younger than 12 years of age with impaired renal function should receive an initial fexofenadine hydrochloride dosage of 30 mg daily.

Since the pharmacokinetics of fexofenadine appear not to be altered in patients with hepatic impairment, the manufacturer states that dosage adjustment is not necessary in such patients. The manufacturer of Allegra-D® (extended-release tablets containing fexofenadine hydrochloride in fixed combination with pseudoephedrine hydrochloride) does not make specific recommendations for dosage adjustment in patients with hepatic impairment, although it is not known if pharmacokinetics of pseudoephedrine are altered in patients with hepatic impairment.

Preparations

Fexofenadine Hydrochloride

Oral

Capsules	60 mg	**Allegra®**, Aventis
Tablets, film-coated	30 mg	**Allegra®** (with povidone), Aventis
	60 mg	**Allegra®** (with povidone), Aventis
	180 mg	**Allegra®** (with povidone), Aventis

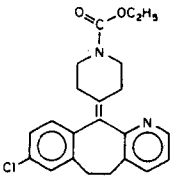
Fexofenadine Combinations

Oral

Tablets, extended-release layer (pseudoephedrine hydrochloride only), film-coated	60 mg with Pseudoephedrine Hydrochloride 120 mg	**Allegra-D®** Aventis

Loratadine

Sch 29851



Chemistry and Stability

■ Chemistry

Loratadine is a tricyclic antihistamine. The drug is a derivative of azatadine, and is related structurally to cyproheptadine. Loratadine differs from azatadine by the presence of a carboxyethyl ester moiety on the piperadine ring and an 8-chloro group on the benzocycloheptapyridine tricyclic ring structure. Conversion of the basic tertiary amino function of azatadine to a neutral carbamate results in compounds, including loratadine, that are less basic and more polar than the parent drug, decreasing their distribution into the CNS. Although the ethyl carbamate derivative has about 1/80th the potency of azatadine, the addition of an 8-chloro group to the tricyclic ring of this compound to form loratadine increases its potency fourfold, and substantially increases its duration of action. Loratadine occurs as a white to off-white powder and is insoluble in water but very soluble in alcohol, acetone, and chloroform.

The rapidly disintegrating loratadine tablets differ from the conventional tablet formulation; both dosage forms contain 10 mg of the drug in each tablet, and are administered orally, but the rapidly disintegrating tablets are flavored and disintegrate within seconds after placement on the tongue, allowing the tablet contents to be swallowed with or without water. The fixed-combination tablets formulated for 12-hour dosing (Claritin-D® 12 Hour) contain 5 mg of loratadine and 60 mg of pseudoephedrine sulfate in an immediate-release outer shell and 60 mg of pseudoephedrine sulfate in an extended-release matrix core that slowly releases the drug whereas the fixed-combination tablets formulated for 24-hour dosing (Claritin-D® 24 Hour) contain 10 mg of loratadine in an immediate-release outer shell and 240 mg of pseudoephedrine sulfate in an extended-release matrix core that slowly releases the drug.

■ Stability

Loratadine syrup, tablets, rapidly disintegrating tablets, and fixed-combination loratadine and pseudoephedrine sulfate extended-release tablets should be stored in tight, light- resistant containers. Loratadine tablets should be stored at 2–30°C and the syrup, rapidly disintegrating tablets, and fixed-combination extended-release tablets formulated for 12-hour dosing should be stored at 2–25°C. The fixed-combination extended-release tablets formulated for 24-hour dosing should be stored at 15–25°C.

Loratadine preparations commercially available in blister packages for individual and institutional use should be stored in a dry place and protected from excessive moisture; the fixed-combination extended-release tablets formulated for 24-hour dosing and commercially available in unit dose blister packages for institutional use also should be protected from light. Loratadine rapidly disintegrating tablets commercially available in blister packages should be used within 6 months of opening the laminated foil pouch enclosing each blister card, and each tablet should be used immediately after opening an individual blister; individual rapidly disintegrating tablets that are not used immediately after opening the blister should be discarded.

Pharmacology

Loratadine is a long-acting antihistamine. The drug has been characterized as a specific, selective peripheral H_1-receptor antagonist and has been referred to as a relatively "nonsedating" or second generation antihistamine. The pharmacology of loratadine resembles that of other currently available antihistamines; however, the overall pharmacologic profile of loratadine differs from that of these other drugs. Experimental evidence indicates that the drug exhibits competitive, specific, and selective antagonism of histamine H_1-receptors. Although the exact nature of loratadine's interaction at the H_1-receptor is unknown, disposition of the drug suggests that the prolonged nature of loratadine's antagonism of histamine may result from the drug's slow dissociation from the H_1-receptors or the formation of the active metabolite, descarboethoxyloratadine.

In vitro, loratadine exhibits a threefold greater affinity for peripheral histamine H_1-receptors than it does for those from brain tissues, whereas terfenadine (no longer commercially available in the US) exhibits a similar affinity for H_1-receptors from peripheral and brain tissues. In vivo, unlike sedating or first generation antihistamines, loratadine does not readily cross the blood-brain barrier and therefore does not appear to interact appreciably with H_1-receptors within the CNS. The presence of a carboxyethyl ester moiety in loratadine may limit distribution of the drug into the CNS, with a resultant decreased potential for adverse CNS effects (e.g., sedation) and anticholinergic effects compared with many other antihistamines. The incidence of CNS effects (e.g., sedation, impaired psychomotor performance) associated with loratadine in clinical studies is similar to that with placebo or terfenadine (no longer commercially in the US) and less than that with currently available sedating or first generation antihistamines (e.g., azatadine, chlorpheniramine, clemastine). Although the incidence of drowsiness in patients receiving the recommended 10 mg dose of loratadine is similar to that in patients receiving placebo, dose-related drowsiness may occur in patients receiving 20–40 mg of the drug. Administration of a single 10 mg dose of loratadine does not appear to impair visual-motor coordination or cause subjective CNS impairment, and administration of a single 10 or 20 mg dose or of repeated 10-mg daily doses of loratadine does not appear to impair driving performance. However, administration of higher than recommended doses (e.g., 20 mg daily over 4 days) can result in substantial impairment of driving performance in some individuals. (See Cautions: Nervous System Effects.)

Unlike many other currently available antihistamines, loratadine has low affinity for cholinergic receptors in vitro, and does not possess appreciable anticholinergic effects at doses exceeding those required for antihistaminic activity in pharmacologic studies. In clinical studies of individuals receiving loratadine, anticholinergic-like effects (e.g., dryness of the nose, mouth, throat, and/or lips) either did not occur or occurred with a frequency similar to that for individuals receiving placebo. Loratadine was a more potent inhibitor of

Pediatric Precautions

Safety and efficacy of glycerin ophthalmic solution in children have not been established.

Carcinogenicity

Studies to evaluate the carcinogenic potential of glycerin have not been performed to date.

Pregnancy, Fertility, and Lactation

Animal reproduction studies have not been performed with glycerin. It is also not known whether the drug can cause fetal harm when administered to pregnant women or affect reproduction capacity. Glycerin should be used during pregnancy only when clearly needed.

Since it is not known if glycerin is distributed into milk, the drug should be used with caution in nursing women.

Dosage and Administration

Administration

Glycerin is administered orally. Headache may be prevented or relieved by having the patient lie down during and after oral administration of the drug. The incidence of nausea and vomiting following oral administration may be minimized by administering a 50% solution of glycerin in 0.9% sodium chloride flavored with a tart citrus base such as lemon juice, or by administering a commercially available flavored 50% glycerin solution. The flavored solution may be poured over cracked ice and sipped through a soda straw.

Sterile anhydrous glycerin is applied topically to the eye. Since glycerin may cause pain and/or irritation following topical application to the eye, a topical local anesthetic should be instilled shortly before administration of glycerin ophthalmic solution.

Dosage

The usual oral dose of glycerin is 1–1.8 g/kg. Additional doses may be administered at approximately 5-hour intervals. When glycerin is used preoperatively, it should be administered 60–90 minutes before surgery.

To reduce superficial corneal edema to facilitate ophthalmoscopic and gonioscopic examination, 1 or 2 drops of glycerin ophthalmic solution may be instilled onto the eye before the examination. In gonioscopic examination of an edematous cornea, additional glycerin ophthalmic solution may be used as the lubricant. For reduction of corneal edema resulting from trauma or disease, 1 or 2 drops of glycerin ophthalmic solution has been instilled onto the eye every 3 or 4 hours.

Preparations

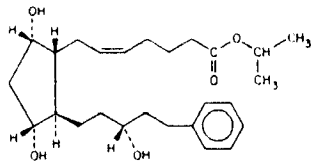
Glycerin

Oral		
Solution	50% v/v (0.628 g/mL)	**Osmoglyn®** (with potassium sorbate; in lime-flavored vehicle), Alcon
Glycerin (Anhydrous)		
Ophthalmic		
Solution		**Ophthalgan®** (with chlorobutanol), Wyeth-Ayerst

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Latanoprost

PhXA41



Chemistry and Stability

Chemistry

Latanoprost, a synthetic analog of naturally occurring prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is an ocular hypotensive agent. The drug differs structurally from $PGF_{2\alpha}$ by the presence of an isopropyl group at the carboxylic acid terminal, the presence of a saturated double-bond between carbon 13 and 14, and substitution of a phenyl ring for part of the omega chain. Esterification of the carboxylic acid terminal of $PGF_{2\alpha}$ increases lipophilicity resulting in better corneal penetration following topical administration, and the phenyl group improves ocular tolerability. Latanoprost is a prodrug and has little, if any, pharmacologic activity until hydrolyzed in vivo to latanoprost acid. Latanoprost, also known as PhXA41, is one of several 17-phenyl substituted isopropyl ester analogs of $PGF_{2\alpha}$ that have been investigated for use as ocular hypotensive agents. While initial studies focused on PhXA34, an equimolar mixture of 15*R* and 15*S* epimers of a 17-phenyl substituted $PGF_{2\alpha}$ analog, subsequent studies focused on latanoprost which is the 15*R* epimer of PhXA34. Because the 15*S* epimer has about 10% of the activity of the 15*R* epimer, latanoprost is about twice as potent as PhXA34.

Latanoprost occurs as a colorless to slightly yellow oil. Latanoprost is freely soluble in alcohol and practically insoluble in water, having a solubility of 200 mg/mL in alcohol and 50 µg/mL in water at 25°C. The estimated pK_a of the drug is 4.88.

Commercially available latanoprost ophthalmic solution is a clear, colorless, isotonic solution of the drug in sterile water for injection; benzalkonium chloride is added as a preservative. The ophthalmic solution is buffered with monobasic sodium phosphate and dibasic sodium phosphate, and sodium chloride is added to adjust tonicity. Commercially available latanoprost ophthalmic solution has a pH of approximately 6.7 and an osmolality of 275 mOsm/kg.

Stability

Unopened bottles of latanoprost ophthalmic solution should be refrigerated at 2–8°C and protected from light. When stored as directed, the ophthalmic solution has an expiration date of 18 months following the date of manufacture. The bottle in use may be stored at room temperature for up to 6 weeks but should not be exposed to temperatures exceeding 25°C.

Pharmacology

Latanoprost, a synthetic isopropyl ester analog of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is a selective prostanoid agonist. Latanoprost is a prodrug of latanoprost acid and has little, if any, pharmacologic activity until hydrolyzed in vivo to latanoprost acid. Naturally occurring $PGF_{2\alpha}$ is a potent FP subtype receptor agonist that also has appreciable agonist activity at some other prostanoid receptors including EP and TP subtypes. Latanoprost acid is highly specific for and has high affinity for the FP subtype prostanoid receptor and, to a lesser extent, the EP_1 subtype prostanoid receptor.

Ocular Effects

Latanoprost is a potent ocular hypotensive agent. Following topical application to the eye and in vivo conversion to latanoprost acid, the drug reduces both elevated and normal intraocular pressure (IOP) in patients with or without glaucoma. In patients with elevated IOP, topical latanoprost can produce mean IOP reductions of about 23–35% from baseline. In healthy individuals with normal IOP or patients with normal-pressure (low-tension) glaucoma, the drug can produce IOP reductions averaging 19–25% from baseline. In dose-ranging studies evaluating commercially available latanoprost ophthalmic solution, maximum reduction in IOP occurred with a topical latanoprost dosage of 1.5 µg daily (i.e., 1 drop [30 µL] of latanoprost ophthalmic solution 0.005% once daily). Administration of topical latanoprost twice daily does not result in a greater reduction in IOP than administration of the drug once daily and may paradoxically reduce the IOP-lowering effect of the drug. In adults with open-angle glaucoma or ocular hypertension, once daily topical administration of latanoprost effectively lowers IOP during the night and day. While results from one study indicated that once daily topical administration of latanoprost in the evening reduces mean diurnal IOP to a greater extent than administration in the morning, results of other studies have not shown such a difference.